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Clinical and Ultrastructural Findings in Three Patients With Geleophysic Dysplasia

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Geleophysic dysplasia, a rare disorder with autosomal-recessive inheritance, is characterized by short stature with a "happy-looking" facial appearance. Nonskeletal findings, particularly in an advanced stage, include hepatosplenomegaly and valvular cardiopathy. Based on the clinical picture and the detection of lysosome-like inclusions in hepatocytes, the underlying cause of the condition is considered to be a storage defect in the metabolism of glycoproteins. The clinical course, with progressive worsening of the condition favors this hypothesis. We report on 3 further cases, in which light and electron microscopic studies of iliac crest biopsies and cultured skin fibroblasts provided additional evidence that geleophysic dysplasia represents a lysosomal storage disease. The additional discovery of storage vacuoles in chondrocytes and skin fibroblasts strongly suggests that the condition is a generalized storage defect. To date, it has not yet been possible to identify the presumed biochemical defect in the metabolic pathways of glycoproteins.

KEY WORDS: geleophysic dysplasia, storage disease, electron microscopy, iliac crest biopsy, skin fibroblasts

INTRODUCTION

Geleophysic dysplasia is a rare congenital disorder first described by Spranger et al. [1971], and finally delineated as an entity by Spranger et al. [1984]. To date, 19 cases have been reported [Vanace et al., 1960; Spranger et al., 1971, 1984a,b; Koiffman et al., 1984; Lipson et al., 1987; Shohat et al., 1990; Wraith et al., 1990; Rosser et al., 1995]. The condition is characterized by short stature with short, thick hands, and a "happy-looking" facial appearance. The nose is short and the upper lip flat with a thin vermilion border and turned-up corners of the mouth. Other typical manifestations are a thick skin and joint contractures. Liver and spleen are enlarged, and valvular cardiopathy restricts the patient's life expectancy. Already on the occasion of its first description [Spranger et al., 1971], it was postulated that the condition might be a lysosomal storage disease. So far, however, neither the storage defect nor the substrate have been identified.

We report on 3 further cases, 2 sibs age 8 and 9 years, and a 12-year-old boy with geleophysic dysplasia. The underlying morphology of the storage defect is demonstrated by analyzing iliac crest biopsies and cultured skin fibroblasts.

CLINICAL REPORTS

Patient 1

Both parents and 2 older sibs of the boy are healthy and of normal stature. After an uneventful pregnancy, delivery took place spontaneously in week 39 with an unusually large amount of amniotic fluid. The limbs with thick hands and feet were noted immediately. He had a bulging forehead, hypertelorism, and an upward slant of palpebral fissures. Birth weight was normal, but length was only 44 cm. The boy started to walk at age 15 months; physical and mental development was normal.

Clinical Findings

The patient's mental development was normal for his age 11 7/12 years). He presented with short stature, with height of 127 cm corresponding to the 3rd centile, and weighing 26.4 kg (Fig. 1). The limbs were moderately short, and his hands and feet were short and thick. The nasal root was broad and the nose short and wide. He had a mild upward slant and epicanthic folds. His mouth was small and thin-lipped. The skin was thickened. The abdominal muscles were well-developed.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

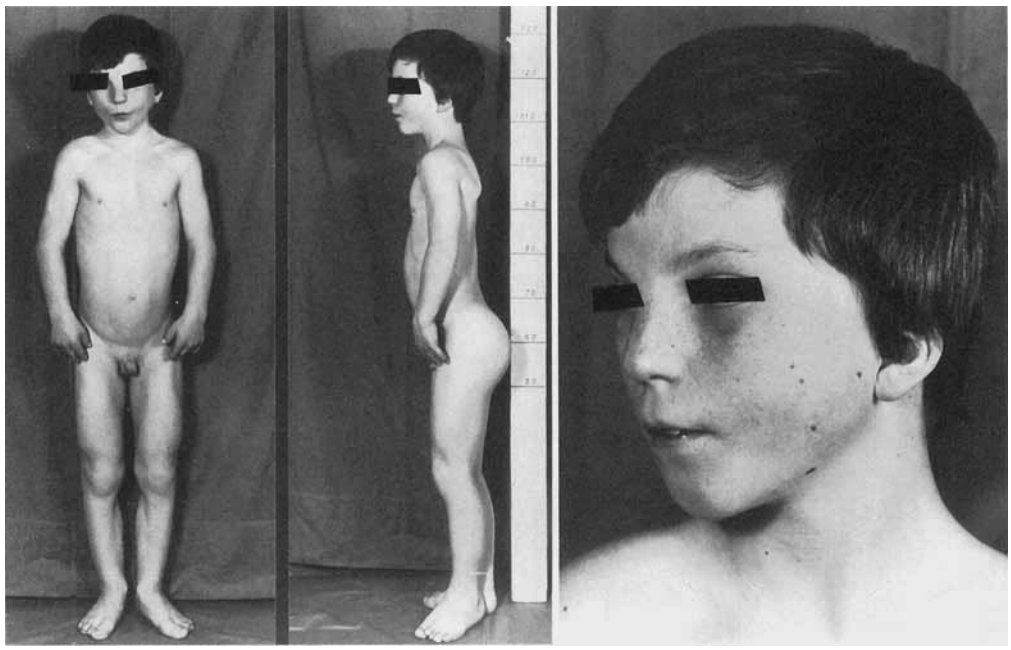

Fig. 1. Patient 1 at age 11 7/12 years. Note patient's position on the tip of the toes with his trunk bent forward.

Joint mobility was generally restricted, and the boy could only stand with his pelvis tilted forward. He was unable to make a fist. A systolic murmur could be auscultated. Neither liver nor spleen appeared enlarged on palapation.

Abdominal ultrasound study showed a liver of normal size but with a dense structure. The spleen was slightly enlarged. Ultrasound also documented stenosis of the abdominal aorta.

X-Ray Findings

Radiological examination demonstrated open cranial sutures and some tiny Wormian bones in the region of the lambdoid suture (not shown). Radii and ulnae were thick and short. The small tubular bones, particularly of the second and fifth fingers, were also short and thick (Fig. 2). The metacarpals were thick, with clearly visible notching. Bone age of the hand corresponded to the child's age. Roentgenograms of the pelvis showed steep acetabular roofs with irregular lower margins of the iliac bones. The shortened femoral necks were in a coxa valga position (Fig. 3).

Patient 2

The parents of the boy, now age 8 7/12 years, are healthy, of normal stature, and have unremarkable body proportions. After a normal pregnancy, the patient was born 4 weeks preterm (birth weight 3,600 g, length 50 cm). Both statomotoric and mental development were unremarkable.

Clinical Findings

The patient was a friendly, normally-developed boy with short stature; his height was 118.5 cm (3rd centile) and he weighed 24 kg (90th centile). He had hypertelorism, a broad, thick nose, and downturned corners of the mouth. He was astigmatic and myopic. His limbs were short, with broad and thick hands and feet. Elbows, wrists, and finger joints presented restricted mobility. Internal organs were unremarkable.

Patient 3

The third patient is the younger sister of patient 2. She was delivered at term after a normal pregnancy. The baby weighed 3,080 g and was 50 cm long. Her statomotoric and mental development was normal.

Clinical Findings

The 7 11/12-year-old girl measured only 106 cm (3rd centile) and weighed 19.1 kg (90th centile). Her head was broad and there was hypertelorism, slight epicanthus, and a thick nose. Like her brother, she was myopic. The limbs were short, and the hands and feet were thick and broad. At time of examination, mobility of the joints was unrestricted. Internal organs were unremarkable.

X-Ray Findings

Bone age corresponded to chronological age and, as in the case of the older brother, the tubular bones of the fingers and metacarpals were short and thick.

Laboratory Findings

Results of routine laboratory investigations (electrolytes, phosphate, and alakaline phosphatase) were normal in all 3 patients.

Urine analysis provided no evidence of a metabolic disorder affecting the amino acids, complex carbohydrates, or oligosaccharides.

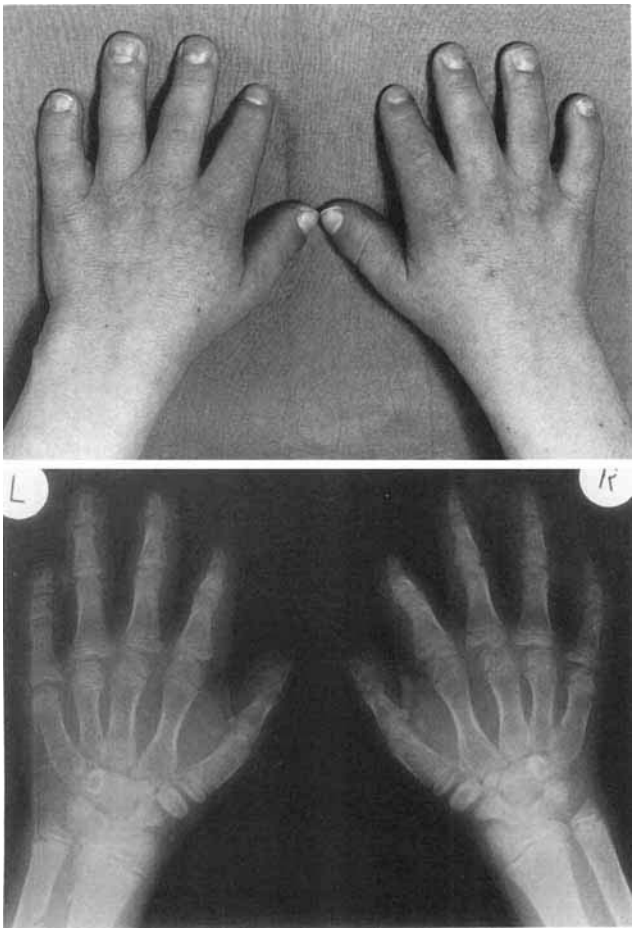

Fig. 2. Patient 1, photograph and radiographs of the hands.

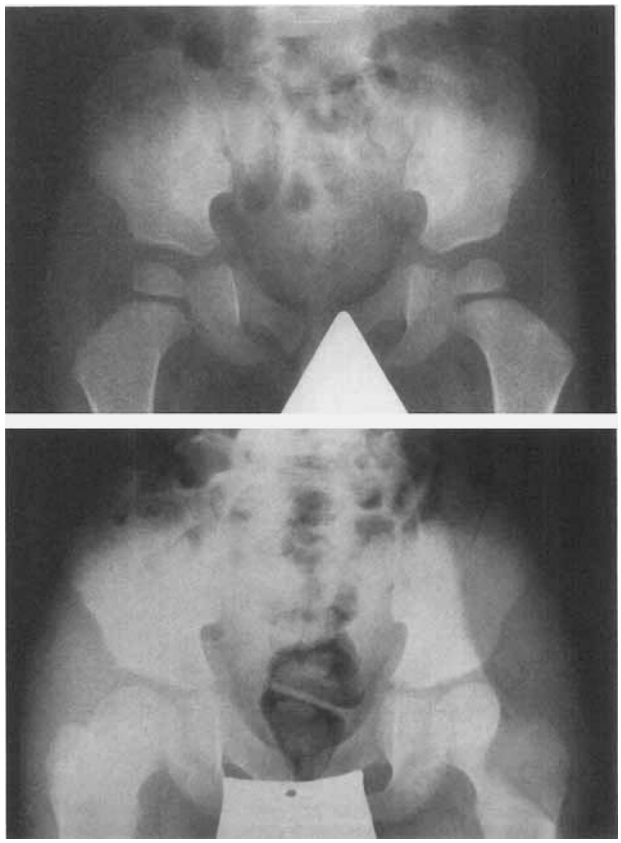

Fig. 3. Patient 1, roentgenogram of the pelvis at age 3½ years **(top)** and 11⁷⁄₁₂ years **(bottom)**. Note short femoral necks in coxa valga position and steep acetabular roofs.

In patient 1, lysosomal enzyme activities were determined in skin fibroblasts and found to be normal.

Collagen types I and III, synthesized by cultured fibroblasts according to the method of Pontz et al. [1982], showed no impairment of the metabolism of these structural proteins. The synthesis ratio of types I and III collagen was unremarkable, and the electrophoretic migratory pattern was normal (by SDS-polyacrylamide-electrophoresis; SDS-PAGE).

Since the clinical findings of patient 3 were unequivocal, it was decided to spare her the stress of special examinations.

MATERIALS AND METHODS

Iliac crest biopsies from patients 1 and 2 were fixed in Schaffer's solution for histology and in 1% glutaraldehyde-4% formaldehyde solution for transmission electron microscopy (TEM). The examination was performed on undecalcified material embedded in methacrylate for histological examination, and in a modified low-viscosity epoxy resin for electron microscopy [Spurr, 1969; Schulz, 1977].

Morphological Findings

Light microscopy (not shown) demonstrated a moderate hypercellularity of the resting cartilage with, in part, vacuolized chondrocytes, several containing pyknotic nuclei. In the PAS Alcian blue staining, intracytoplasmic alcianophilic deposits were seen. The ground substance showed a reduction in mucopolysaccharides. In the proliferation zone the chondrocytes were reduced in number. The growth plate was only incompletely modelled and contained short, thick columns of chondrocytes.

TEM showed a perichondrium with very densely-packed collagen fibrils, which, in part, showed marked differences in diameter. The cartilage matrix was composed of collagen fibrils of variable length and width, interwoven into a netlike structure (Fig. 4b). Some of these collagen fibrils had typical cross-striations, but some were only inadequately aggregated. The cytoplasm contained varying numbers of vacuoles; sectionwise these appeared as lysosomal vacuoles, a few containing fine, granular, slightly osmiophilic material (Fig. 4a). The Golgi apparatuses were enlarged, and the mitochondria were swollen. In some sections atypical, amanthoid-like collagen fibrils were observed in the cartilage lacunae. The bony tissue was unremarkable.

Skin fibroblasts cultured from patients 1 and 2 were also examined by TEM. The cultured fibroblasts were enlarged compared to controls. The endoplasmic reticulum was moderately dilated. The cytoplasm contained many, very densely-packed lysosomal storage vacuoles

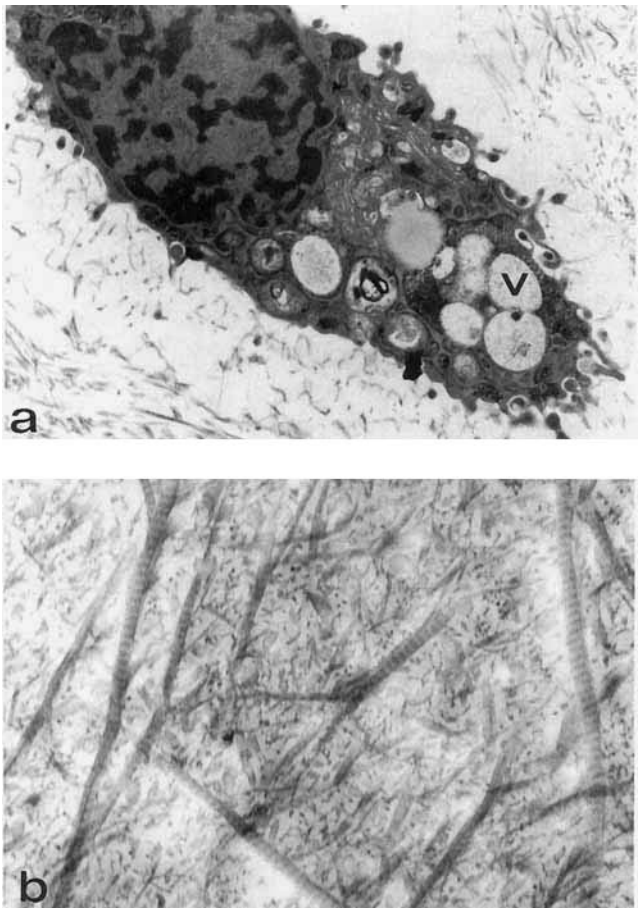

Fig. 4. Iliac crest biopsy of patient 1. **a:** Chondrocyte with lysosomal-like storage vacuoles (v) in the cytoplasm, containing fine granular material (TEM, ×9,000). **b:** Cartilage matrix with irregularly-arranged thin and broad collagen fibrils (TEM, ×17,000).

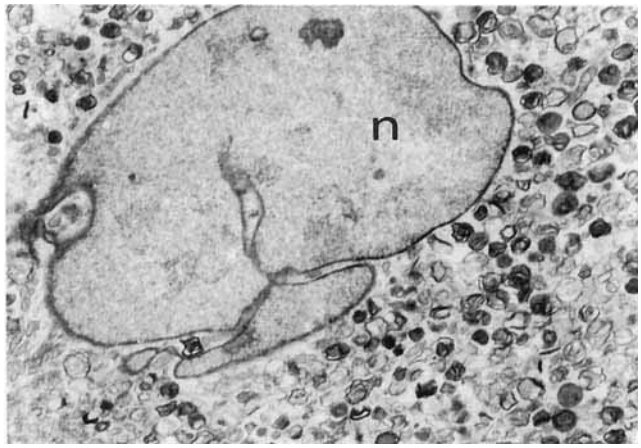

Fig. 5. Cultured skin fibroblast of patient 1, with numerous lysosomal-like storage-vacuoles, several containing lamellar structures (n, nucleus) (TEM, ×5,000).

sectionwise (Fig. 5). These contained abundant inclusions, with a predominately lamellar structure.

DISCUSSION

On the basis of observations made so far, one can presume that geleophysic dysplasia affects both sexes and is an autosomal-recessive trait [Koiffman et al., 1984]. Patients present with short stature with short, thick hands and feet. Joint contractures, cardiac valve defects, hepatosplenomegaly, and thickened skin are also observed. The diagnosis is usually suspected shortly after birth on the basis of these manifestations. At birth the children are often of normal size or slightly below normal size. So far, a prenatal ultrasound diagnosis of such children has not been possible [Rosser et al., 1995]. Short stature manifests only later during the course of the disease.

Lysosomal storage phenomena have already been described in liver tissue [Spranger et al., 1984; Lipson et al., 1987]. For the first time, our examinations demonstrate storage phenomena in cartilage tissue and cultured skin fibroblasts. The stored substance is apparently a glycoprotein. The underlying molecular defect remains unknown. The discovery of storage phenomena in chondrocytes and cultured skin fibroblasts suggests that the condition is a generalized storage disease and not, as had been supposed, a focal or local disease of the liver, spleen, and cardiac valves [Spranger et al., 1984a; Lipson et al., 1987]. The storage phenomena in cartilage might explain disturbed cartilage growth, causing short stature. The clinical course favors the hypothesis of a generalized disease with variable expression, similar to other congenital metabolic disorders.

The condition of acrofacial dysplasia described by Spranger et al. [1984b] as a disorder resembling geleophysic dysplasia is probably an expression of a variable clinical manifestation of one and the same genetic defect.

The condition of acromicric dysplasia first described by Maroteaux et al. [1986] has similar clinical symptomatology with dwarfism, brachydactyly, and joint contractures. In chondrocytes, increased glycogen storage has been found. However, this syndrome does not include hepatosplenomegaly, valvular cardiopathies, and the "happy-looking" facial appearance of geleophysic dysplasia. Histological and ultrastructural findings described in Maroteaux et al. [1986] show clear differences from the morphological changes we found in geleophysic dysplasia, e.g., absence of lysosomal storage phenomena. Other conditions with acrofacial dysplasia, such as tricho-rhino-phalangeal dysplasia (Langer-Giedeon syndrome), acrodysostosis (a form of pseudohypoparathyroidism), and other conditions with brachydactyly can readily be distinguished clinically and radiologically.

Lipson et al. [1987] suggested that geleophysic dysplasia and several other syndromes with acrofacial dysplasia and acromicric dysplasia, although showing common clinical manifestations such as small hands and feet, should be considered distinct disorders. On the basis of the morphologically detectable storage phenomena in different tissues, geleophysic dysplasia

must be considered a separate entity which can be delineated on the basis of a combination of clinical and morphological findings. In contrast to some other storage diseases, mental development in most patients with geleophysic dysplasia is normal. Due to the cardiac involvement, which usually becomes clinically apparent between 2 and 8 years, the prognosis is poor. The oldest patient is now 18 years old.

Our findings show that geleophysic dysplasia is a lysosomal storage disease manifesting as generalized progressive disease in various organs. Morphological analyses might be helpful in confirming the clinical diagnosis.

REFERENCES

Koiffmann CP, Wajntal A, Ursich MJM, Pupo AA (1984): Familial recurrence of geleophysic dysplasia. Am J Med Genet 19:483–486.

Lipson AH, Kan AE, Kozlowski K (1987): Geleophysic dysplasia—Acromicric dysplasia with evidence of glycoprotein storage. Am J Med Gen [Suppl] 3:181–189.

Maroteaux P, Stanescu R, Stanescu V, Rappaport R (1986): Acromicric dysplasia. Am J Med Genet 24:447–449.

Pontz BF, Krieg T, Müller PK (1982): (+)-cyanidanol-3 changes functional properties of collagen. Biochem Pharmacol 31:3581–3589.

Rosser EM, Wilkinson AR, Hurst JA, McGaughran JM, Donnai D (1995): Geleophysic dysplasia: A report of three affected boys—Prenatal ultrasound does not detect recurrence. Am J Med Genet 58:217–221.

Schulz A (1977): A reliable method of preparing undecalcified human bone biopsies for electron microscopic investigation. Microsc Acta 80:7.

Shohat M, Gruber HE, Pagon RA, Witcoff LJ, Lachman R, Ferry D, Flaum E, Rimoin DL (1990): Geleophysic dysplasia: A storage disorder affecting the skin, bone, liver, heart and trachea. J Pediatr 117:227–232.

Spranger J, Gilbert EF, Tuffli GA, Rossiter FP, Opitz JM (1971): Geleophysic dwarfism: A "focal" mucopolysaccharidosis? Lancet 2: 97–98.

Spranger J, Gilbert EF, Arya S, Hoganson GMI, Opitz JM (1984a): Geleophysic dysplasia. Am J Med Genet 19:487–499.

Spranger J, Gilbert EF, Flatz S, Burdelski M, Kallfelz HC (1984b): Acrofacial dysplasia resembling geleophysic dysplasia. Am J Med Genet 19:501–506.

Spurr AR (1969): A low-viscosity resin embedding for electron microscopy. J Ultrastruct Res 26:31.

Vanace PW, Friedman S, Wagner BM (1960): Mitral stenosis in an atypical case of gargoylism. Circulation 21:80–89.

Wraith JE, Bankier A, Chow CW, Danks M, Sardharwalla JB (1990): Geleophysic dysplasia. Am J Med Genet 35:153–156.